Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 28-60 are pending in the application, with claims 28-31 being the independent claims. Claims 1-27 have been canceled without prejudice to or disclaimer of the subject matter thereof. Claims 28-60 have been added. Support for new claims 28-60 can be found throughout the specification and in the original claims.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Objection under 37 C.F.R. § 1.75(c)

The Examiner has objected to claims 5-22 and 27 under 37 CFR § 1.75(c) as being in improper form because a multiple dependent claim cannot depend on another multiple dependent claim. (Office Action, section 1). Applicants respectfully traverse this objection.

Claims 5-22 and 27 have been canceled. Applicants direct the Examiner's attention to the Preliminary Amendment which was filed on December 23, 1998, concurrently with the above-captioned application. In the preliminary amendment, claims 5-8, 17, 21 and 27 were amended to eliminate multiple dependencies. These

amendments simultaneously corrected the dependencies for claims 9-16, 18-20, and 22. Thus, all of claims 5-22 and 27 are properly dependent. Applicants respectfully submit that the Examiner's objection under 37 C.F.R. § 1.75(c) has been overcome and should be withdrawn.

Applicants specifically request that the Examiner issue a supplemental, non-final office action examining all pending claims including claims 37-54 and 59 which are directed to the subject matter of original claims 5-22 and 27 which were improperly objected to and thus not examined.

II. Rejections under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected claims 1-4 and 23-26 under 35 U.S.C. § 112, second paragraph, as being indefinite. (Office Action, section 3, lines 1-3). Applicants respectfully traverse this rejection.

A. First Stated Grounds for Rejection

The Examiner has rejected claim 1 "as indefinite because the instantly claimed method lacks a final process step that clearly relates back to the preamble." (Office Action, section 3, lines 4-5). The Examiner is further of the opinion that:

> For the method of claim 1, the preamble of the instantly claimed method is drawn to a process for determining the pharmacological effect of a substance on the activity of various biological target molecules while the

> final process step is that of using different detection methods directly compared with one another in step b(ii) and it is thus unclear as to whether the instantly claimed methods are drawn to a process for determining the pharmacological effect of a substance on the activity of various biological target molecules or rather using different detection methods directly compared with one another. Method claim requires a last step or phrase in the last step that states the accomplishments of the goals for the method which were stated in the method's preamble. Claim 1 lacks such a last step and are confusing because the additional method step is not sufficiently set forth. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashions. See Ex parte Erlich, 3 USPQ2d 1011, p. 1011 (Bd. Pat. Applicant. Int. 1986). It is suggested that an amended claim more clearly describing the intended steps be submitted.

(Office Action, section 3, lines 5-17). Applicants respectfully disagree.

Claims 1-27 have been canceled. New independent claims 28, 29, 30 and 31 do contain a final process step. Claims 32-60 are dependent claims. Thus, this stated grounds for rejection under 35 U.S.C. § 112, second paragraph, does not apply to any of the present claims.

B. Second Stated Grounds for Rejection

The Examiner has rejected claim 1 "over the recitation of the phrase, 'basic biological constitution.'" (Office Action, section 3, line 18). The Examiner is of the opinion that "[i]t is not clear what kind of constitution is claimed. Are the nucleus, mitochondria, plasma membrane, golgi apparatus and other subcellular compositions claimed or the functional characteristics of particular cells claimed or nucleic acids, proteins and lipids characteristic of a particular kind of cells claimed? The metes and

bounds of the claim is vague and indefinite." (Office Action, section 3, lines 18-22). Applicants respectfully disagree.

Claims 1-27 have been canceled. The phrase "basic biological constitution" has been limited by proviso in claims 28-31, which are the new independent claims. Thus, new claims 28-31 are neither vague nor indefinite. New claims 32-60 are dependent claims which do not contain the phrase "basic biological constitution." Thus, this stated grounds for rejection under 35 U.S.C. § 112, second paragraph, does not apply to any of the present claims.

C. Third Stated Grounds for Rejection

The Examiner has rejected claims 1 "over the recitation of the phrase, 'one operation.'" (Office Action, section 3, line 23). The Examiner is of the opinion that "[i]t is not clear what kind of operation is claimed. Is the whole method carried out in one vessel or in one step or by one person or by a particularly special and innovative methodology. The metes and bounds of the claim is vague and indefinite." (Office Action, section 3, lines 23-26). Applicants respectfully disagree.

Claims 1-27 have been canceled. The phrase "one operation" does not appear in any of new claims 28-60. Thus, this stated grounds for rejection under 35 U.S.C. § 112, second paragraph, does not apply to any of the present claims.

D. Fourth Stated Grounds for Rejection

The Examiner has rejected claim 23 "over the recitation of the phrase, 'in question.'" (Office Action, section 3, line 27). The Examiner is of the opinion that "[i]t is not clear what is the question, who is making the question, what is the answer and who is answering the question. The metes and bounds of the claim is vague and indefinite." (Office Action, section 3, lines 27-29). Applicants respectfully disagree.

Claims 1-27 have been canceled. The phrase "in question" does not appear in any of new claims 28-60. Thus, this stated grounds for rejection under 35 U.S.C. § 112, second paragraph, does not apply to any of the present claims.

D. Summary

Applicants respectfully submit that all of the stated grounds for rejecting claims 1-4 and 23-26 under 35 U.S.C. § 112, second paragraph, have been rendered moot and the rejection should be withdrawn.

III. Rejection Under 35 U.S.C. § 102

The Examiner has rejected claims 1-4, 23-24 and 26 under 35 U.S.C. § 102(b) as being anticipated by Foulkes *et al.* (PCT International Publication WO 92/13063,

published August 6, 1992). (Office Action, section 5, lines 1-2). Applicants respectfully traverse this rejection.

Specifically, the Examiner is of the opinion that:

> Foulkes et al teach a process for determining the pharmacological effect of a substance on the activity of various biological target molecules, wherein a substance is applied to test cells which contain one or more biological target molecules and the effect of the substance on the activity of the target molecules is determined, caracterized in that in one operation a defined amount of a test substance (Claims 67-72 and 104 and Page 56, line 5 to page 61, line 20)
>
> a) is applied to test cells with the same basic biological constitution which differ in that they contain one or more differennt biological target molecules (Claims 67-72 and Claims 92-102 and page 56, Addition of chemicals to cells Subsection); and/or
>
> b) is applied to test cells which contain one or more biological target molecules, the cells differing in that they have different basic biological constitutions (Claims 67-72 and Claims 92-102 and page 56, Addition of chemicals to cells Subsection); and
>
> i) the effect of the substance on the or each biological target molecule is measured using a detection system coupled to the activation of the target molecule (Claims 94-103 and Page 57, line 5 to page 58, line 8); and/or
>
> ii) the effect of the substance on different regulatory mechanisms triggered by the activation of the target molecule is determined by measuring the effects using a plurality of detection systems each coupled to the different regulatory mechanisms, and the effects of the test substance on the different test cells or the effects determined using different detection methods are directly compared with one another (Figure 20 and Page 58, line 13 to page 59, line 12).

(Office Action, section 5, lines 3-21).

The Examiner is further of the opinion that:

> Foulkes et al teach a process characterized in that a plurality of substances, optionally in several dilutions, are applied in parallel to one or more sets of cellular substrates, each set constituting a group of different assays or assay formats based on the same targeting cell

> (Claims 84-87 and page 56, Addition of chemicals to cells Subsection).
>
> Foulkes et al teach a process characterized in that the test cells are mammalian and human cells (Claims 76-79 and Page 42, line 5 to page 43, line 11).
>
> Foulkes et al teach a process characterized in that the test cells contain a reporter gene under the control of a regulatory sequence which responds to the change in the concentration of a messenger substance of a signal transmission pathway, of which the target molecule is a component, and that the effect of the test substance on the target molecule is determined in a change in the expression of the reporter gene (Figures 1-4, 6-9 and 11-12 and Page 57, line 5 to page 58, line 8 and Figures 20-24).
>
> Foulkes et al teach a process characterized in that the reporter gene is luciferase (Figures 1-4, 6-9 and 11-12 and Page 57, line 5 to page 58, line 8).
>
> Foulkes et al teach a process characterized in that the test cells which are dependent on a growth factor for their proliferation are cultivated in the presence of the growth factor and the effect of the substance on the cells is determined by indirectly measuring the apoptosis or the proliferation of the cells (Page 2, line 23 to page 5, line 5 and Page 42, line 5 to page 43, line 11 and Figure 20).

(Office action, section 5, lines 22-40).

Claims 1-27 have been canceled and replaced by new independent claims 28-31 and new dependent claims 32-60.

The screening methods of the present invention are directed to "a process for determining the pharmacological activity of a substance on the activity of different biological target molecules" (*see*, e.g., page 4, lines 15-17, and claim 1, at page 53, lines 4-6, of the application as filed). These target molecules are receptor proteins (*see, e.g.*, page 12, lines 21-30 of the application as filed). In contrast to the present invention, the screening methods disclosed by Foulkes *et al.* are methods "of determining whether a molecule not previously known to be a modulator of protein biosynthesis is capable of

transcriptionally modulating the expression of a *gene encoding a growth factor*" (*see, e.g.*, page 32, lines 17-21, page 33, lines 12-16, page 34, lines 4-8, claim 71 at page 92, lines 3-7 and claim 72 at page 93, lines 93, lines 31-35) (emphasis added). Foulkes *et al.* does not teach screening for other than a molecule not previously known to be a modulator of protein biosynthesis which is capable of transcriptionally modulating the expression of a gene encoding a growth factor. Therefore, Foulkes *et al.* does not anticipate any of the pending claims.

New claims 28 and 30 are directed to a process for screening using test cells that have been derived from a single type of tissue and a single species. In contrast to the present invention, Foulkes *et al.* does not teach the requirement that the screening process be conducted using test cells that have been derived from a single type of tissue and a single species. Therefore, Foulkes *et al.* does not anticipate independent claims 28 or 30 or any claims dependent thereon.

IV. Rejections Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 1-4 and 23-26 under 35 U.S.C. § 103(a) over Foulkes *et al.* in view of Chapman *et al.* (U.S. Patent No. 6,232,099 B1, issued on May 15, 2001). Applicants respectfully traverse this rejection.

A. The Primary Reference (Foulkes et al.)

The Examiner is of the opinion that "Foulkes *et al.* teach the process of claims 1-4, 23-24 and 26 as described above." (Office Action, section 7, line 4). Applicants respectfully disagree. The Examiner is further of the opinion that "Foulkes *et al.* do not teach the Green fluorescent protein as the reporter gene." (Office Action, section 7, line 5).

Claims 1-27 have been canceled and replaced by new independent claims 28-31 and new dependent claims 32-60.

The screening methods of the present invention are directed to "a process for determining the pharmacological activity of a substance on the activity of different biological target molecules" (*see*, e.g., page 4, lines 15-17, and claim 1, at page 53, lines 4-6, of the application as filed). These target molecules are receptor proteins (*see, e.g.,* page 12, lines 21-30 of the application as filed). In contrast to the present invention, the screening methods disclosed by Foulkes *et al.* are methods "of determining whether a molecule not previously known to be a modulator of protein biosynthesis is capable of transcriptionally modulating the expression of a *gene encoding a growth factor*" (*see, e.g.,* page 32, lines 17-21, page 33, lines 12-16, page 34, lines 4-8, claim 71 at page 92, lines 3-7 and claim 72 at page 93, lines 93, lines 31-35) (emphasis added). Foulkes *et al.* does not teach or suggest screening for other than a molecule not previously known to be a modulator of protein biosynthesis which is capable of transcriptionally modulating

the expression of a gene encoding a growth factor. Therefore, claims 28-60 are not obvious in view of Foulkes *et al.* and the other reference cited by the examiner..

New independent claims 28 and 30 are directed to a process for screening using test cells that have been derived from a single type of tissue and a single species. In contrast to the present invention, Foulkes *et al.* does not teach or suggest the requirement that the screening process be conducted using test cells that have originated from a single type of tissue and a single species. Therefore, Foulkes *et al.* and the other reference cited by the Examiner do not render obvious new independent claims 28 or 30 or any claims dependent thereon.

B. The Secondary Reference (Chapman et al.)

The Examiner is of the opinion that:

> Chapman et al teach the Green fluorescent protein as the reporter gene (Examples 1 and 2 and Figures 1a and 1b).
>
> It would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to combine and substitute the Green fluorescent protein of Chapman et al. in the process of Foulkes et al., since Chapman et al. state, "The green fluorescent protein (GFP) from A. Victoria is a reporter of gene expression in heterologous systems. GFP has an advantage over other marker proteins in that it can be detected non-invasively, without any requirement for exogenous substrates or co-factors since it fluoresces intrinsically without a requirement for exogenous substrate. In addition, fluorescence of GFP is retained in fusion proteins allowing the subcellular localization of fusion proteins (Column 7, line 66 to column 8, line 7)." An ordinary practitioner would have been motivated to combine and substitute the Green fluorescent protein of Chapman et al. in the process of Foulkes et al. in order to improve the process for determining the pharmacological effect of a substrate on a cell and also in order to achieve the express

> advantages, as noted by Chapman et al., of a protein which has an advantage over other marker proteins in that it can be detected non-invasively, without any requirement for exogenous substrates or co-factors since it fluoresces intrinsically without a requirement for exogenous substrate and in addition, fluorescence of which is retained in fusion proteins allowing the subcellular localization of fusion proteins.

(Office Action, section 7, lines 6-23). Applicants respectfully disagree.

Claims 1-27 have been canceled and replaced by new independent claims 28-31 and new dependent claims 32-60.

In contrast to the present invention, Chapman *et al.* does not teach or suggest a process for determining the pharmacological activity of a substance on the activity of different biological target molecules. Thus, the deficiencies in Foulkes *et al.* are not cured by Chapman *et al.* Therefore, claims 28-60 are not obvious in view of Chapman *et al.* or the other reference cited by the Examiner.

In contrast to the present invention, Chapman *et al.* does not teach or suggest the requirement that the screening process be conducted using test cells that have originated from a single type of tissue and a single species. Thus, the deficiencies in Foulkes *et al.* are not cured by Chapman *et al.* Therefore, Chapman *et al.* and the other reference cited by the examiner do not render obvious new claims 28 or 30 or any claim dependent thereon.

C. Summary

Applicants respectfully submit that the rejection of claims 1-4 and 23-26 under 35 U.S.C. § 103(a) has been overcome and should be withdrawn.

Conclusion

All of the stated grounds of objection and rejection having properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

In the claims:

Claims 1-27 have been canceled without prejudice or disclaimer.

Claims 28 to 60 have been added.